REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1 to 12 and 14 to 17 are pending. Claims 13 and 18 to 25 have been previously cancelled. No claims are amended herein.

Interview Summary.

Examiner Petterolf graciously granted a telephonic Interview on January 8, 2008. The discussion focused on claim 10, the prior art disclosure and relevant case law.

Applicant's representative, Gary Baker, noted that the Melvin WO 97/12246 reference does not teach all limitations of claim 10. Applicant's representative noted that *In re Best*, cited in the rejection, requires that the prior art teach a subject material before Applicants are required to prove a novelty critical function. Applicant's representative noted that the burden of *In re Best* does not apply in the present case because the cited prior art does not teach the same material, and function of the material is not critical to novelty of the claim.

The Examiner did not contradict statements, but suggested Applicants confirm the cited prior art does not teach monoclonal antibodies to the claimed antigens.

Allowed Claims.

Applicants appreciate that claims 1 to 9 have been determined to be in condition for Allowance.

35 U.S.C. §102.

Claims 10 to 12 and 15 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Melvin et al., (WO 97/122460). To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. That is, in order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v. Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983).

As a preliminary matter, Applicants note that the rejection of claim 10, based on alleged anticipation by Melvin, has been previously made and withdrawn by the Office. The present claim 10 is unchanged from that time. In response to the present rejection, Applicants provide herein, essentially the same remarks as were provided in the Response of January 19, 2007. In addition Applicants provide further notes on the applicability of "inherency" case law to the present facts.

In the Response to the first Office action, Applicants noted "Melvin describes preparation of polyclonal antibodies against CYP1B1 in rabbits using oligopeptides specifically not those of the present claims (see page 9). Melvin mentions that polyclonal or monoclonal antibodies suitable for use [in immunohistochemistry assays for CYP1B1 antigen] can be obtained according to conventional procedures.

Melvin does not teach all the limitations of claim 10. With regard to the preparation of polyclonal antibodies, Applicants reiterate the arguments [of the 1/19/07 Response] presented with regard to the rejection for alleged anticipation by Pottenger. Applicants note that Western blot detection of CYP1B1 in Melvin using polyclonal antibodies raised against oligopeptides [15-mers conjugated to keyhole limpet hemocyanin (KLH)] specifically not included in the present claims shows that polyclonal detections of CYP1B1 does not necessarily require the presence of antibodies specifically binding the sequences cited in claim 10. Applicants note the facts show that Melvin did not raise any polyclonal or monoclonal antibodies against the specific sequences of claim 10.

Because Melvin did not raise polyclonal or monoclonal antibodies to whole CYP1B1 or to the polypeptides cited in claim 10, the rejection can only hinge on the teaching at page 9 of Melvin, that methods exist in the universe to raise antibody preparations against CYP1B1. Such a rejection can not stand because this does not expressly or inherently teach, e.g., an isolated monoclonal antibody that recognizes an epitope that binds to the specific amino acid sequences VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, where x is D or N and y is L or F.

Applicants note that preparation of monoclonal antibodies to whole CYP1B1 does not necessarily provide the isolated monoclonal antibodies of claim 10, and therefore the claim is not anticipated by Melvin. Monoclonal antibodies are generally isolated by, e.g.,

exposing a mouse to an antigen of interest, harvesting activated B-lymphocytes from the spleen of the mouse, fusing the lymphocytes with immortal cells to form a hybridoma possibly expressing a single antibody to a single epitope of the antigen, screening the hybridomas for expression of an antibody of interest and cloning a hybridoma expressing an antibody of interest. Should one create monoclonal antibodies starting with the CYP1B1 sequences of Melvin, no antibody of claim 10 could possibly result. Should one create a monoclonal antibody starting with exposure of the mouse to full-length CYP1B1, a monoclonal antibody ultimately produced would not necessarily be directed to an epitope of the cited amino acid sequences. Therefore, Melvin can not be considered to anticipate the present claims according to the holding of *Continental Can Co.* For example, the monoclonal antibody produced would not be directed to the cited epitopes including the amino acid sequences of the claim if: 1) the cited sequences were not sufficiently immunogenic to the mouse (e.g., not "foreign" enough or not adequately presented on the CYP1B1 protein), 2) if B-lymphocytes of interest fail to fuse with the immortal cells to form viable hybridomas, 3) if the screening method for hybridoma clones was not specific for cells producing antibodies against the cited amino acid sequences or were unsuccessful (note - Melvin did not teach a specific clone screening method that would provide the claimed antibodies), and/or 4) if the hybridomas selected in the screening did not include the cited amino acid sequences or failed to grow in the cloning step. Any given monoclonal randomly raised against full length CYP1B1 would be unlikely to be specific to the cited amino acid sequences; and screening techniques to specifically select the cited sequences are not taught in the art. Typically, efforts to raise monoclonal antibodies to an antigen do not result in isolation of antibodies to epitopes including all sequences of an antigen. Monoclonal antibodies prepared against CYP1B1 would not inherently recognize any particular epitope of CYP1B1, and certainly not inherently recognize epitopes of the sequences cited in claim 10. Therefore, the rejections for alleged anticipation based on Melvin must be withdrawn." Emphasis added.

The Office acknowledges in the present Action, page 2, that Melvin does "not explicitly teach that the monoclonal antibodies recognize an epitope in the cytochrome P450 CYP1B1 protein included within the amino acid sequence VNQWSVNHDPVKWPN or

PExFDPARFLDKDGy ..." However, the Office alleges "the claimed antibody appears to be the same as the prior art ..." because there is homology between human, rat and mouse CYP1B1 sequences. Based on these statements, the Office notes that the PTO does not have facilities to establish whether the prior art material is the same or not, and asserts the "burden is on the applicant to prove that the claimed product is different from those taught by the prior art ..." The Action cites *In re Best*, 562 F2d 1252; 195 USPQ 430(CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1992.

Ex parte Gray holds that where there is doubt whether the prior art product is the same as the claimed product, it can be the burden of the applicant to prove a difference. However, because there is no doubt that the prior art product is different from the claimed product, Applicant is not required to prove a difference. There is no doubt that the rabbit polyclonal antibodies in Melvin, to different sequences, are not the presently claimed isolated monoclonal antibodies. There is no doubt Melvin did not produce any monoclonal antibodies that could be tested. There is not doubt that the theoretical monoclonal antibody production from whole CYP1B1 inoculation would not necessarily result in isolation of the presently claimed specific monoclonal antibodies.

In re Best, states that "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the Examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102 / 103 rejection. [That is, one can not claim a preexisting composition based on a previously unknown function of the composition. Further,] where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." Emphasis added. *In re Best* is not on point with the present facts. The actual and conceptual compositions taught by Melvin are not the same as the specifically claimed product. Moreover, the functional aspect is not critical to establishing novelty. For example, the structural aspect of the amino acid sequences are novel in the context of the claims.

Even if the burden had shifted to Applicants to prove the claimed compositions are not inherent in the cited art, this is an easy burden to meet, as described above. For example, it is clear the rabbit polyclonal antibodies are not the isolated monoclonal antibodies. Monoclonal antibodies theoretically isolated from mice inoculated with whole CYP1B1 could be against epitopes other than those of the claims, and thus are not inherent from the teachings of Melvin, as discussed above.

Because Melvin does not teach isolated monoclonal antibodies recognizing epitopes of VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, where x is D or N and y is L or F, Applicants respectfully request withdrawal of the section 102 rejections.

35 U.S.C. §103(a).

Claims 10 to 12 and 15 were rejected under 35 U.S.C. §103(a) as allegedly obvious based on Pottenger (Arch. Biochem. Biophys. 286:488; 1991) in light of Campbell (Monoclonal Antibody Technology, Elsevier Science, pp. 1-33; 1986). Claims 16 and 17 were rejected under 35 U.S.C. §103(a) as allegedly obvious based on Melvin in light of Chiocca (U.S. 5,688,773). Claim 14 was rejected under 35 U.S.C. §103(a) as allegedly obvious based on Melvin in light of Queen (WO 90/07861) and Kettleborough (Protein Engineering 4: 773-783, 1991). Applicants traverse.

It is notable that the monoclonal antibodies of the inventive compositions have the special feature that they do not cross react with other members of the CYP family of proteins, so are useful, e.g., in specifically identifying cells expressing CYP1B1, e.g., without false positives from cells expressing, e.g., only CYP1A1. One generically preparing monoclonal antibodies from whole CYP1B1 would be unlikely to stumble upon this feature without the benefit of impermissible hindsight.

A proper analysis under the recently reaffirmed *Graham v John Deere* standard demonstrates the non-obviousness of the invention. The Graham factors include:

(A) Determining the scope and content of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

The Foccarino memo further notes that the "teaching-suggestion-motivation (TSM) test was *not* overturned by *KSR*. In addition, the bulk of well established case law, such as described in MPEP 2143.01 still applies. For example, where the cited references teach away from the invention it is not obvious. The combination of references must teach all of the elements of the claims, the Office must provide a clear and articulated reason motivating one of skill to make the proposed combination, and there must exist in the art a reasonable expectation of success in any proposed combination. Here, the rejection fails each of these requirements, as applied to the *Graham* factors.

Claims are not obvious based on Pottenger and Campbell. Pottenger is said to teach polyclonal antibodies to P450-EF. Campbell is cited as teaching it is "customary now ... to make monoclonal antibodies to" identified macromolecules.

The allegations of the Action do not state a case. Routine customary preparation of monoclonal antibodies to the full length P450-EF sequence does not teach one in the art to prepare the present compositions. That is, the difference between the cited prior art and the claims is such that one of skill would not have obviously provided the specific compositions of the invention. The cited art is generic and does not point to the present invention. Further, the provided antigen is large and would provide a variety of possible hybridoma clones to any number of epitopes. Based on the generic, and different, teachings one would not obviously prepare the specific monoclonal antibodies of the invention.

The Office cites *Ex parte Erlich* for the position that "once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious." In *Erlich*, product by process generic hybridoma cells were deemed obvious in light of the known starting generic antigen. The claims in *Erlich* covered any hybridoma cells producing antibodies to any part of the isolated INF antigen. However, it is well-established law that the genus does not teach the species. Here, the species of antigen at issue has not been isolated in the cited art, but is an unidentified needle hidden in the haystack of epitopes in the full length cytochrome. *Erlich* actually states "it is our finding that once the antigen of interest is selected, the use of that antigen in the known method ... will result in the expected ... specific monoclonal antibodies." Emphasis added. The "antigen of interest" in Pottenger is full length P450-EF and the expected monoclonal antibody would be a randomly generated

against one of any number of P450-EF epitopes. Pottenger does not select the specific antigens of the claim or expect an antibody to the specific epitopes; so the composition is not obvious according to *In re Erlich.*

Because the dependent claims include all limitations of the claim upon which they depend, none of the dependent claims can be considered obvious.

Yes, monoclonal technique existed before the present invention. Yes, CYP1B1 existed before the present invention. But no combination of references expressly or inherently teaches one of skill to provide the specific isolated monoclonal antibodies binding the specific epitopes as required by the present claims. Therefore, Applicants respectfully request the rejections based on Pottenger be withdrawn.

Claims are not obvious based on Melvin and Chiocca. Melvin does not teach all limitations of the independent claim 10, as discussed above. Even assuming Melvin teaches monoclonal antibodies to CYP1B1, this does not direct one of skill to the monoclonal antibodies of the invention designed to bind the previously undisclosed specific epitopes, e.g., with unexpected minimal cross-reactivity with other members of the CYP protein family. Again, a genus does not describe a species, and teaching CYP1B1 monoclonal antibodies generally does not teach or motivate the production of the specific monoclonal antibodies of the invention.

Chiocca does not cure the failure of Melvin to teach all limitations of the independent claim 10. At least because dependent claims include all limitations of the claim upon which they depend, claims 16 and 17 are not obvious. Therefore, Applicants respectfully request withdrawal of the rejections based on Melvin and Chiocca.

Claims are not obvious based on Melvin in light of Queen and Kettleborough. As discussed above, Melvin does not teach all limitations of the independent claim 10. Even assuming Melvin teaches monoclonal antibodies to CYP1B1, this does not direct one of skill to the monoclonal antibodies of the invention which are designed to bind the previously undisclosed specific epitopes with unexpected minimal cross-reactivity with other members of the CYP protein family.

Queen and Kettleborough do not cure the failure of Melvin to teach all limitations of the independent claim 10. At least because dependent claims include all

limitations of the claim upon which they depend, claim 14 is not obvious. Therefore, Applicants respectfully request withdrawal of the rejections based on Melvin. Queen and Kettleborough.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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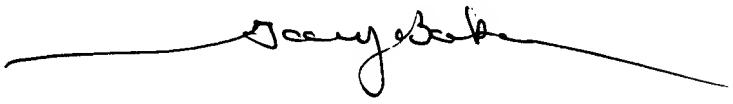
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for **1** month;
2) A transmittal sheet;
3) A fee transmittal sheet; and,
4) A receipt indication postcard.